Different Effect of the Pure Na\(^+\) Channel-Blocker Pilsicainide on the ST-Segment Response in the Right Precordial Leads in Patients With Normal Left Ventricular Function

Takeshi Ueyama, MD; Akihiko Shimizu, MD*; Toshihiko Yamagata, MD**; Masahiro Esato, MD; Masato Ohmura, MD; Yasuhiro Yoshiga, MD; Masashi Kanemoto, MD; Ryousuke Kametani, MD; Akira Sawa, MD; Shinsuke Suzuki, MD; Naoki Sugi, MD; Masunori Matsuzaki, MD

**Background** The response of the ST-segment in the right precordial leads to Na\(^+\) channel blockers in patients without structural heart disease and a typical Brugada-type ECG has not been fully elucidated.

**Methods and Results** A pilsicainide challenge test was performed in 161 patients and according to recently established ECG criteria and an organized computer algorithm, the ST morphology was classified and the maximum increase in the J wave amplitude (max\(\Delta J\)) from the standard and right precordial leads V1–3 was examined. Before the test, subjects exhibiting type 1 ECG in the standard leads were excluded. After administering pilsicainide, type 1 ECGs in the standard leads were observed in 31 cases and a max\(\Delta J\) of \(\geq 200\mu V\) was observed in 29 cases (23 type 1, 2 type 2/3 and 4 normal ECGs). In the additional higher right precordial leads, type 1 ECGs were observed in 55 cases and a max\(\Delta J\) of \(\geq 200\mu V\) was observed in 45 cases (42 type 1 and 3 type 2/3 ECGs).

**Conclusions** A max\(\Delta J\) \(\geq 200\mu V\) induced by pilsicainide, including that measured in the high right precordial leads, was associated with a change mainly to a type 1 ECG. (Circ J 2007; 71: 57–62)

**Key Words:** Brugada syndrome; Brugada-type ECG; Drug challenge test; Pilsicainide; ST-segment

Although Na\(^+\) channel blockers are widely used for various arrhythmias in clinical practice, they can unmask the Brugada-type ECG and further induce elevation of the ST-segment, which can sometimes lead to ventricular tachyarrhythmias in patients with Brugada syndrome (BS). The response of the ST-segment to Na\(^+\) channel blockers in structurally normal hearts has seldom been discussed because the main effects of Na\(^+\) channel blockers on the ECG are QRS and QT prolongation. Recent-
Table 1 Clinical Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>95</td>
</tr>
<tr>
<td>Symptom related arrhythmias</td>
<td>57</td>
</tr>
<tr>
<td>Syncope or fainting</td>
<td>38</td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td>66</td>
</tr>
<tr>
<td>ECG abnormalities with a Brugada sign</td>
<td>58</td>
</tr>
<tr>
<td>Arrhythmias*</td>
<td>8</td>
</tr>
</tbody>
</table>

*: 1 atrial premature contractions, 6 ventricular premature contractions and 1 paroxysmal supraventricular tachycardia.

Table 2 The Value of the J Wave Amplitude in the Right Precordial Leads and QRS Width Before and After Pilsicainide

<table>
<thead>
<tr>
<th></th>
<th>Before (n=95)</th>
<th>After (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (ΔJ)</td>
<td>72±48</td>
<td>102±111</td>
</tr>
<tr>
<td>V2 (ΔJ)</td>
<td>153±70</td>
<td>259±155*</td>
</tr>
<tr>
<td>V3 (ΔJ)</td>
<td>128±65</td>
<td>204±95*</td>
</tr>
<tr>
<td>1h V1 (ΔJ)</td>
<td>60±53</td>
<td>90±118</td>
</tr>
<tr>
<td>1h V2 (ΔJ)</td>
<td>132±87</td>
<td>236±193*</td>
</tr>
<tr>
<td>1h V3 (ΔJ)</td>
<td>124±66</td>
<td>214±116*</td>
</tr>
<tr>
<td>2h V1 (ΔJ)</td>
<td>35±47</td>
<td>58±104</td>
</tr>
<tr>
<td>2h V2 (ΔJ)</td>
<td>82±67</td>
<td>151±152*</td>
</tr>
<tr>
<td>2h V3 (ΔJ)</td>
<td>106±63</td>
<td>191±131*</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>96±11</td>
<td>120±12*</td>
</tr>
</tbody>
</table>

Before: before the pilsicainide administration; after, after the pilsicainide administration; Vn, right precordial lead Vn (n=1–3); 1h Vn, right precordial lead 1 intercostal space above lead Vn (n=1–3); 2h Vn, right precordial lead 2 intercostal spaces above lead Vn (n=1–3).

and defined as types 1, 2 and 3 according to the Heart Rhythm Society and the European Heart Rhythm Association! We used these ECG criteria and excluded subjects exhibiting type 1 ECGs in the standard leads in the control state. We also excluded patients with VT (≥triplets), or a family history of BS or sudden unexpected death. All cases then underwent echocardiography with careful attention paid to any right ventricular (RV) enlargement and/or wall motion abnormalities and were also checked for conditions that may lead to ST-segment elevation. Therefore, patients with organic heart disease or other factors that may have influenced ST-segment elevation were excluded.

All patients gave written informed consent to participate in the study, which was approved by the Institutional Clinical Research and Ethics Committee.

Na+-Channel-Blocker Challenge Test

We performed a Na+-channel-blocker challenge test using pilsicainide, a so-called pure Na+-channel blocker, in a room with a defibrillator and life support facilities. Pilsicainide was administrated intravenously at a speed of 0.1 mg·kg⁻¹·min⁻¹ over 10 min (total 1 mg/kg) with continuous ECG and non-invasive blood pressure monitoring. During drug administration, we monitored the ECG using the standard 12 leads, but after performing 96 tests, we began monitoring not only the standard right precordial leads V1–3, but also those recorded from 1 intercostal space (ICS) higher than the right precordial leads using the V4–6 electrodes, because in several cases we found marked ST elevation after the pilsicainide test in the higher right precordial leads only. Drug administration was immediately stopped when ST elevation (≥0.5 mV), extensive QRS prolongation, unfavorable symptoms and/or frequent ventricular arrhythmias were observed. In this study, the test was considered positive if the abnormal coved-type ECG pattern (type 1 ECG) appeared in more than 1 right precordial lead.

Electrocardiography

Before and after the administration of pilsicainide, we recorded the standard 12-lead ECG (ECG-9322, Nihon Kohden Corp, Tokyo, Japan). The J wave amplitude (STJ (ΔJ)) was analyzed by an organized computer algorithm (ECAPS 12C, Nihon Kohden). In the ECAPS 12C, the terminal point of the QRS (J point) was defined as the offset point of the QRS waveform determined from the averaged QRS waveforms from the 12 leads. After the drug test, we calculated the increase in the STJ (ΔJ) in each of the right precordial leads (V1–3). The maximum increase in the STJ (maxΔJ) was defined as the maximum value of ΔJ of the 3 leads. Based on the ECG criteria, we defined it as either a “Brugada-type” type 1 ECG (coved type with an STJ ≥200 mV), or “suspect Brugada-type” type 2/3 ECG (saddle-back type with an STJ ≥200 mV), and these were reviewed by 2 independent cardiologists. The other ECGs without these criteria were defined as “normal”, including Brugada “like” ECGs of either the coved or saddle-back type with an STJ <200 mV and non-specific ST elevation with an STJ ≥200 mV. As described in the primary consensus report, an increase in the J wave amplitude of greater than 200 mV was also considered a significant diagnostic value, and we assessed the prevalence of ST morphology and maxΔJ, with a cutoff point defined as 200 mV in the high right precordial leads during Na+-channel blocker administration.

ECG From the High Right Precordium

To evaluate the ST-segment recorded from the high right precordium in all cases, we moved the 3 leads 1 or 2 ICS higher after making baseline recordings from the standard leads before and after pilsicainide. From all the ECGs recorded, including those from the higher placement of leads, we assessed the maxΔJ and ST morphology.

Statistical Analysis

Data are given as the mean±SD. The ECG data were analyzed by paired t-test. The chi-square test for independence was used for comparisons of the prevalence of a type 1 ECG after giving pilsicainide in 2 groups divided by a cutoff point of 200 mV for the maxΔJ. A value of p<0.05 was considered statistically significant.

Results

Pilsicainide Dose and Effect on J Wave Amplitude and QRS Width

In the 161 cases, the administration of pilsicainide was stopped in 21 when the ST junction in the right precordial leads became elevated by more than 0.5 mV and/or the number of VPCs and couplets increased. The mean dose was 0.97 mg/kg. Severe complications, such as VT or VF, did not occur.

Pilsicainide increased the STJ in each lead, and a significant increase in leads V2 and V3 recorded from both the standard and higher positions was especially noted. The QRS width was significantly prolonged in all patients (Table 2).
Prevalence of the Brugada-Type ECG Before and After Drug Challenge Test

Before the administration of pilsicainide, suspicious Brugada-type ECGs (type 2/3) were observed in 20 cases (12%). After the administration of pilsicainide, Brugada-type ECGs (type 1) were observed in 31 cases (19%), which at baseline were type 2/3 ECG in 8 cases and normal ECG in 23 cases.

Including the recordings from the higher placement of the leads, in 10 cases a type 1 ECG before pilsicainide was documented, which in the baseline standard leads had been a type 2/3 ECG in 6 cases and normal ECG in 4 cases.

After pilsicainide, 24 more cases had a documented type 1 ECG, which in the standard leads was a type 2/3 ECG in 5 cases and normal ECG in 19 cases (Fig 1).

Distribution of the Maximum Increase in the STJ

In the standard ECG leads, a maxΔJ ≥200μV was observed in 29 cases (type 1 ECG in 23 cases, type 2/3 ECG in 2 cases, normal ECG in 4 cases) after pilsicainide (Fig 2). In 5 of 6 cases that did not exhibit a type 1 ECG, a type 1 ECG could be detected when the right precordial leads were moved higher.

When the high right precordial leads were included, 16 more cases, which had a maxΔJ <200μV in the standard leads, had a maxΔJ ≥200μV. In 42 of 45 cases with a maxΔJ ≥200μV in which the higher leads were included, the ECG exhibited a type 1 ECG. In contrast, the maxΔJ in all the patients with a normal ECG after the pilsicainide test, even when recording from the higher leads, did not exceed 200μV. The prevalence of ST-segment morphology with a maxΔJ greater than and less than 200μV significantly differed for both recording methods (Fig 2). Further, there were no normal ECGs with a maxΔJ ≥200μV in the analysis of the additional higher leads (Fig 2). A representative case of a type 1 ECG in only the higher leads after pilsicainide is shown in Fig 3. Each value of the maxΔJ for each type of ST-segment morphology after pilsicainide,
including those for the additional higher leads, is plotted in Fig 4. Note that there were no patients with a max $\Delta J \geq 200 \mu V$ in the normal ECGs after pilsicainide. In Fig 4 $200 \mu V$ max $\Delta J$ represents the cutoff line and value that was used to divide the distribution of the normal ECGs from abnormal ECGs after pilsicainide.

**Discussion**

In the present study, we assessed the prevalence of a Brugada-type (type 1) ECG and the increase in the J wave amplitude in the right precordial leads, including higher placement of the leads, in order to evaluate the effects of pilsicainide on the ST-segment in the ECGs not exhibiting a type 1 ECG in the standard leads during the control state. We found that the prevalence of a type 1 ECG after pilsicainide was 19% and the prevalence of a max $\Delta J \geq 200 \mu V$ after the test was 18% in the standard leads. By recording from the right precordial leads, the prevalence of a type 1 ECG after pilsicainide increased by 9% (an additional 14 cases) and the prevalence of a max $\Delta J \geq 200 \mu V$ after the test increased by 10% (an additional 16 cases) compared with using only the standard leads. The majority of cases (23 of 29 in the standard leads and 42 of 45 in the high right precordial leads) with a max $\Delta J \geq 200 \mu V$ exhibited a typical type 1 ECG. In contrast, cases that showed no obvious morphological ST-T changes (normal ECGs), even when the high right precordial leads were used in the analysis, had an increase in the amplitude of less than 200 $\mu V$. To the best of our knowledge, there have been few reports describing evidence of positive criteria for the Na$^+$ challenge test. Our data supports the positive criteria of the pharmacologic test in the consensus report$^4$ and an increase in the J wave amplitude of greater than 200 $\mu V$ seems to have a meaningful significance for the diagnosis of a drug-induced BS compatible ECG.

**Na$^+$-Channel-Blocker Challenge Test Using Pilsicainide**

It has been widely accepted that a shift in the balance of the current, which leads to the loss of the action potential dome in the RV outflow epicardium but not the endocardium, is the mechanism of ST elevation in the right precordial leads in BS.$^{13}$ With a reduction in the inward Na$^+$ currents (INa), the notch in the epicardial action potentials becomes deeper, producing a voltage gradient between the epicardium and endocardium. This voltage gradient produces ST elevation in the right precordial leads and induces lethal arrhythmias caused by phase 2 reentry.$^{13}$ Induction of VF during the drug challenge test or after the administration of Na$^+$-channel blockers in patients with paroxysmal atrial fibrillation with typical ST-segment elevation has been described.$^{3,14,15}$ However, we carefully administered pilsicainide with continuous ECG monitoring and immediately discontinued administration when marked ST-segment elevation, excessive QRS prolongation or ventricular arrhythmias were observed. We completed the drug challenge test safely without any severe adverse events.$^4,9$

Recently, an association of BS with atrial fibrillation, atrial vulnerability and supraventricular tachyarrhythmias has been reported.$^{16-18}$ Therefore, we performed the drug
challenge test not only in those who exhibited ECG abnormalities, but also in those who had some symptoms and/or various arrhythmias in order to diagnose drug-induced Brugada-type ECGs and/or to evaluate the safety of the drug. We used pilsicainide, which is a pure Na+ -channel blocker and class Ic drug based on the Vaughan Williams classification. Other class I anti-arrhythmic agents have ion channel blocking effects not only on the Na+ channels but also on K+ channels including the transient outward current (Ito), which mediates the spike-and-dome morphology of the epicardial action potential. By using a pure Na+ channel blocker, changes in the ST-segment morphology, as viewed on the ECG, may directly reflect the drug’s blocking effect on the Na+ channel.

In regard to the assessment of the J wave amplitude, it is often difficult to determine the J point, especially with the Brugada sign, because of the obscurity of the end of the QRS and the beginning of the T wave. In order to avoid any error in the measurement using manual measurements, we performed a quantitative analysis using a computer algorithm.

Effects of Pilsicainide on ST-Segment Morphology and Elevation

In BS, some investigators have reported that the Brugada sign is more easily detected from the higher right precordium than in the usual standard ECG recording positions. However, Priori and Napolitano found that this maneuver led to an over-diagnosis of BS. Further, the augmentation of ST-segment elevation by Na+ channel blockers may not be a specific response solely for BS. Peters et al reported that 16% of patients with RV cardiomyopathy responded with ST elevation to the Na+ channel challenge test and Goda et al reported pilsicainide-induced coronary vasospasms in a patient with a Brugada-type ECG. It also appears to be necessary to have a type 1 ECG after pilsicainide administration in order to differentiate a normal variant from BS.

There have been few reports about the prevalence of drug-induced Brugada-type ECGs in a relatively large group of patients with structurally normal hearts or in a healthy population. Hong et al investigated the response to the ajmaline test in 4 large families with SCN5A mutations. The incidence of a positive test was high in the genetic carriers and low in the genetic non-carriers. Because we did not routinely perform genetic tests, it is unclear whether there was a relationship between the pilsicainide test and the genetic test.

Clinical Implications and Study Limitations

Because the observed drug-induced changes are surrogate for a genetic diagnosis of BS, the true meaning of a positive challenge is unknown and, therefore, of uncertain significance. However, because the present study showed that the ECG response to Na+ channel blockers exhibited a distinct difference in both the ST-T morphology and response of the J wave amplitude in the majority of cases, we believe that using the pilsicainide challenge test according to our method makes it possible to discriminate between a drug-induced Brugada-type ECG and normal variants.

It is still now an important issue as to whether or not the Na+ channel challenge test can stratify the risk of cardiac events, so that we can give adequate recommendations or suggestions to our patients. In our study, the patients with an unmasked coved-type ST elevation are all alive. We still need a long-term follow-up of those patients to determine whether or not they will develop cardiac events.

Conclusion

The pilsicainide challenge test performed according to our protocol was safe and helpful for diagnosing drug-induced Brugada-type ECGs. Based on the response recorded in the right precordial leads, including the high right precordial leads, to pilsicainide, a maxAJ ≥200 μV was associated with a change mainly to a type 1 ECG. In this group there should be great concern for the possible risk of lethal arrhythmias.

References